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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/706,738
Filing Date: November 12, 2003
Appellant(s): HILFINGER ET AL.

Avery N. Goldstein
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 2/27/2008 appealing from the Office action mailed 9/17/07.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Niedzinski et al (Lipids 35(7): 721-727, 2000)

Perrie et al (J. Liposome Res. 12(1&2): 185-197, 2002)

Kitadai et al (Brit. J. Cancer 81 (14): 647-653, 1999)

6,627,197	**Keener**	**9-2003**
6,075,012	**Gebeyehu**	**6-2000**

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), in view of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012).

Niedzinski taught cholic acid conjugates comprising a substituted alkyl polyamine DNA binding domain and their use to protect DNA from degradation in the gastric system. Niedzinski envisioned the use of these conjugates to deliver therapeutic nucleic acids by oral delivery to the gastrointestinal system, particularly to the enterohepatic receptors of the small intestine, which recognize and take up bile salts. See abstract, paragraph bridging pages 721 and 722. The cholic acid moieties were esterified through an oxygen at C3 to a DNA binding domain. See scheme 1 on page 722, compounds 5 and 6. Niedzinski showed the conjugates could be used to deliver plasmids to non-gastric cells, i.e. NIH 3T3 fibroblasts (see paragraph bridging pages 725 and 726, and Fig 5 on page 726).

Niedzinski did not teach the use of cholestanol, coprostanol, glycocholic acid, chenodeoxycholic acid, deoxycholic acid, glycochenodeoxycholic acid, taurocholic acid, or taurochenodeoxycholic acid. However, Niedzinski considered his conjugation technique to be applicable to a variety of bile acids through the C3 hydroxyl (see last sentence of column 1 on page 724). Niedzinski also did not teach DNA binding domains comprising peptides.

Keener taught the use of bile acids, and cholesterol derivatives generally, as hydrophobic conjugates to aid in the cellular entry of a conjugated peptide (a proricin variant). Proricin is hydrophilic and so does not readily traverse cell membranes. Keener overcame this problem by conjugation of a hydrophobic moiety, such as a sterol or bile acid, that facilitates traversal of the cell membrane. Disclosed hydrophobic groups included bile acids and cholesterol derivatives such as cholic acid, coprostanol,

glycocholic acid, chenodeoxycholic acid, deoxycholic acid, glycochenodeoxycholic acid, and taurocholic acid. See column 19, lines 37-55.

Thus it was clear to one of ordinary skill in the art at the time of the invention that bile acids and cholesterol derivatives were recognized as exchangeable, equivalent hydrophobic groups useful for facilitating the transfer of conjugated hydrophilic groups into cells.

Gebeyehu taught reagents and methods for intracellular delivery of nucleic acids. The reagents are cationic lipids with the general formula of ABZ, wherein A is a steroid such as the bile acid cholic acid, or the sterols stigmasterol or ergosterol, B is a linker, and Z can be a nucleic acid binding domain such as a substituted alkyl polyamine (Z_4-Z_8, column 7, lines 44-67) or a polycationic peptide (protamine, a histone, or other nucleic acid binding protein). See column 9, line 62 to column 10, line 10 first, then column 3, lines 50-64; column 4, lines 50-54; column 5, lines 36 and 52-58; and scheme 8 at columns 29 and 30. Accordingly, it was clear to those of ordinary skill in the art at the time of the invention that it was routine to conjugate nucleic acid binding domains to cholesterol derivatives to make nucleic acid delivery conjugates, and that substituted alkyl polyamines and polycationic nucleic acid binding peptides such as protamines and histones were exchangeable equivalent nucleic acid binding domains.

It would have been obvious to one of skill in the art at the time of the invention to substitute any hydrophobic bile acid or cholesterol derivative for the cholic acid of Niedzinski. One of ordinary skill at the time of the invention would have had a reasonable expectation that modified bile acids would be recognized and taken up by

the appropriate receptors because Niedzinski taught that this occurred for C(3)-modified cholic acid. There is no reason of record to expect that other bile acids would not function similarly.

One of ordinary skill at the time of the invention would also have recognized that bile acids and sterols were recognized as functioning as hydrophobic moieties that can facilitate delivery of a conjugated hydrophilic moiety to cells. Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute other bile acids and sterols for cholic acid in the conjugates of Niedzinski, inasmuch as one would reasonably expect these conjugates to be taken up by the enterohepatic receptors that normally function in uptake of bile acids, and to function as transfection-facilitating hydrophobic groups even in the absence of receptors.

One of ordinary skill would recognize from the teachings of Niedzinski, Keener, and Gebeyehu that the hydrophobic nature of the bile acid and sterol conjugates would facilitate the traversal of lipid bilayers even in the absence of a bile acid receptor (as demonstrated by Niedzinski with NIH 3T3 cells). Hence one would have had a reasonable expectation of success in substituting these equivalent hydrophobic moieties for each other. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07 indicates

that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

It would also have been obvious to one of ordinary skill in the art at the time of the invention to substitute a nucleic acid binding peptide for the nucleic acid binding polyamine of Niedzinski because these nucleic acid binding moieties were recognized in the art as equivalents in view of the teachings of Gebeyehu, i.e. polyamines are equivalents of polycationic nucleic acid binding peptides. See MPEP 2144.06.

Regarding claim 20 and the ‘Y’ linker peptide moiety, the first 2 or 3 amino acids of the DNA-binding peptide of Gebeyehu (histone, protamine or DNA binding protein) can arbitrarily be considered to be the linker peptide.

Regarding claim 30, the cited art did not explicitly teach a commercial package comprising the composition and instructions for use. However, Gebeyehu did teach kits comprising the compositions. See column 13, lines 18-24. It would have been obvious to one of ordinary skill in the art at the time of the invention to place the components of such a kit into a container. One would have been motivated to do so in order to organize the components into an easily retrievable state. One would have been motivated to include instructions because one of ordinary skill in the art appreciates that referring to instructions decreases the frequency of errors. Thus the invention as a whole was prima facie obvious.

Thus the invention as a whole was prima facie obvious.

Claims 15 and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012) as applied to claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 above, and further in view of Perrie et al (J. Liposome Res. 12(1&2): 185-197, 2002).

Niedzinski, Keener, and Gebeyehu render obvious methods of delivering nucleic acids to target cells of a subject by administering a nucleic acid encoding a protein and a lipidic agent comprising a bile acid or cholesterol derivative conjugated to a polyionic DNA-binding peptide. Niedzinski taught that the DNA/lipidic agent could be formulated with DOTAP and/or DOPE and also with DMDHP and DOPE. See paragraph bridging columns 1 and 2 on page 725, Table 2 on page 726, and Fig. 5 on page 726. Gebeyehu also suggested combination of steroid derived cationic lipids with lipids such as DOPE, DOSPA, DOTMA, or cholesterol for delivery to cells (see column 5, lines 37-45).

These references did not exemplify a composition comprising a therapeutic compound.

Perrie taught oral intragastric delivery of cationic liposome comprising nucleic acids encoding the S (small) region of the hepatitis B surface antigen (HBsAg). DNA vaccines encoding HBsAg were formulated with a cationic lipid formulation (phosphatidylcholine/cholesterol/DOTAP) and administered orally. Immune responses against the antigen were observed. See abstract. The nucleic acid of Perrie is

considered to be a therapeutic product that is antibiotic in nature by virtue of its activity in inducing an immune response against hepatitis B virus.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the conjugate of Niedzinski as modified by Keener and Gebeyehu to deliver any nucleic acid that one wished to express in a cell, regardless of the nature of the expressed protein, because the purpose of these conjugates is to deliver nucleic acids to cells. It would have been similarly obvious to use the conjugates of Niedzinski/Keener/Gebeyehu in the method of Perrie because Niedzinski and Gebeyehu taught that such conjugates could be added to cationic lipids such as DOTAP, and because the conjugate takes advantage of uptake by enterohepatic receptors. See Niedzinski at paragraph bridging columns 1 and 2 on page 725, and Table 2 on page 726, and Gebeyehu at column 5, lines 37-45. Further, Niedzinski showed in Fig. 5 that addition of a bile acid conjugate to a cationic lipid/cholesterol mixture improved transfection.

One of ordinary skill could consider the conjugates of Niedzinski, as modified by Keener and Gebeyehu, to be improved versions of the cholesterol of Perrie, i.e. versions that lend improved DNA binding and delivery characteristics, and would be motivated to substitute them for, or add them to, the cholesterol of Perrie for that reason.

Claims 11, 12, 15, and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), Keener et al (US

Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012) as applied to claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 above, and further in view of Kitadai et al (Brit. J. Cancer 81(14): 647-653, 1999).

Niedzinski, Keener, and Gebeyehu render obvious methods of delivering nucleic acids to target cells of a subject by orally administering a nucleic acid encoding a protein and a lipidic agent comprising a bile acid or cholesterol derivative conjugated to a polyionic DNA-binding peptide. Niedzinski taught that the DNA/lipidic agent could be formulated with DOTAP and/or DOPE and also with DMDHP and DOPE. See paragraph bridging columns 1 and 2 on page 725, Table 2 on page 726, and Fig. 5 on page 726. Gebeyehu also suggested combination with lipids such as DOPE, DOSPA, DOTMA, or cholesterol for delivery to cells (see column 5, lines 37-45).

These references did not teach secretion of an expressed protein, and did not exemplify a composition comprising a therapeutic compound.

Kitadai taught transfection of human gastric carcinoma cells with an expression vector encoding the secreted protein interleukin-8. Transfection was performed using the cationic lipid formulation LIPOFECTIN (a 1:1 mixture of DOTMA and DOPE).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the conjugate of Niedzinski as modified by Keener and Gebeyehu to deliver any nucleic acid that one wished to express in a cell, regardless of the nature of the expressed protein, because the purpose of these conjugates is to deliver nucleic acids to cells.

It would also have been obvious to one of ordinary skill in the art at the time of the invention to use the bile acid conjugate of Niedzinski as modified by Keener and Gebeyehu in the method of Kitadai by adding it to the DOTMA/DOPE formulation (LIPOFECTIN) because Niedzinski taught that a similar conjugate could be effectively added to another DOPE/cationic lipid mixture to improve transfection (Fig. 5).

Also it would have been obvious to use a DOTAP/DOPE/conjugate mixture or a DMDHP/DOPE/conjugate mixture in place of the LIPOFECTIN in the method of Kitadai because such mixtures were intended for gene transfer to cells, and would be functional equivalents of LIPOFECTIN. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

Claims 15 and 16 are included in this rejection because the nucleic acid of Kitadai is considered to be a therapeutic product that is an antitumoral.

(10) Response to Argument

At pages 6-10 of the Brief, Appellant argues that Niedzinski in view of Keener fails to render the A-R_1 moiety obvious in the instant inventive method. The A-R_1 moiety is the cholesterol derivative recited in the claims.

At page 7 top paragraph, Appellant asserts that a person of ordinary skill would not think that multiple bile acids are suitable for delivering a nucleic acid to target cells just because the conjugation technique of Niedzinski is amenable to multiple bile acids. This is unpersuasive for several reasons.

The cholic conjugates of Niedzinski were constructed to target bile salt receptors, and such receptors are efficient at taking up bile salts generally. See the sentence bridging pages 721 and 722, wherein Niedzinski indicated that these receptors took up bile salts with an efficiency of up to 95%. This uptake is not characterized as limited to cholic acid, but is mentioned in the context of bile salts generally, so one of ordinary skill would have had a reasonable expectation that the receptors would function to take up conjugates utilizing cholic acid as well as other bile salts. Niedzinski taught that the C(3) position of cholic acid could be modified without loss of receptor binding, and so placed a DNA-binding domain at that position. One of ordinary skill would have had no reason to believe that the C(3) position of other bile salts would be especially critical for receptor interaction, and so would have had a reasonable expectation of success in substituting other bile acids for cholic acid in the invention of Niedzinski.

Further, one of ordinary skill, aware of the teachings of Keener and Gebeyehu would be well aware that the cholic acid moiety of Niedzinski, as well as other bile acid and sterol moieties generally, would serve as a good hydrophobic group for facilitating the transfer of a conjugated hydrophilic group across a cell membrane, even in the absence of the enterohepatic receptors of Niedzinski. As explained above, this is simply due to the hydrophobic nature of sterols and bile acids (see Keener at column 19, lines 37-55 and Gebeyehu at abstract; column 1, lines 13-24; paragraph bridging columns 1 and 2; and column 9, line 62 to column 10, line 25). This principle is further supported by Niedzinski Fig. 5. This figure shows that the cholic acid conjugates can improve transfection of 3T3 cells which are fibroblasts, not gastric cells, and so would not be expected to express the gastric enterohepatic receptors.

The idea is analogous to that used in the general art of cationic lipid-mediated DNA transfections in which a DNA binding cationic group is attached to a hydrophobic group, such as a diacylglycerol or cholesterol moiety (e.g. DC-Chol, i.e. (cholesteryl-3(beta)N-dimethyl aminoethyl) a widely used cationic lipid transfection reagent). The conjugates of Niedzinski, Keener, and Gebeyehu are simply cationic lipids in which the hydrophobic domain is a cholesterol derivative that is a bile acid or sterol, similar to DC-Chol. In view of the teachings of Keener and Gebeyehu, one of ordinary skill in the art at the time of the invention would have reasonably expected any hydrophobic cholesterol derivative to be able to function as the hydrophobic group in a cationic lipid.

Appellant argues at the paragraph bridging pages 7 and 8 that the rejections of independent claims 8 and 20 fail to satisfy a prima facie case of obviousness because it is “flawed logic to allege that simply because other bile acids are amenable to modification by a sample synthetic strategy that the reference provides adequate support for using un-C(3)-functionalized bile acids as biologically functional agents for the instantly claimed use.” The Examiner understands this as an argument that Niedzinski does not teach modification at positions other than C(3), so one of ordinary skill would have no expectation of success in using cholesterol derivatives modified at positions other than C(3). The relevance of this argument is not clear. The instant claims do not exclude C(3)-modified derivatives, so Applicant appears to be arguing limitations not in the claims. Furthermore, the instant specification explicitly envisions C(3) modification at page 13, line 2, so it is clearly reasonable to determine that C(3) modification is embraced within the claims. Finally, for the recited cholesterol derivatives “cholestanol” and “coprostanol”, the only position available for modification is the C(3) hydroxyl. These compounds lack any other hydroxyl or carboxyl group, so they must be modified at the C(3) position because the specification teaches no other way to modify these compounds.

Further regarding modifications at other positions, it should be noted that Niedzinski stated that the prior art showed that modification could be made to cholic acid at either position 3 or position 24 without interfering with receptor recognition. See page 722, column 1, lines 12-17. Position 24 corresponds to the carboxyl group of cholic acid. Furthermore, Gebeyehu taught an example in which the C(24) carboxyl group of cholic acid is modified to contain a cationic peptide. See column 15, lines 35-44, and Scheme 8 at columns 29 and 30, which gives rise to a cholic acid derivatives modified at C(24) with a cationic group. So, in view of the prior art, one of ordinary skill would reasonably expect that C(24) conjugates could be used to deliver nucleic acids to cells via enterohepatic receptors. Of course, such conjugates would reasonably be expected to deliver nucleic acids to cells simply because of their cationic lipid nature, regardless of the presence of bile salt receptors.

Much of the discussion in the paragraphs bridging pages 7-9 of the Brief focuses on whether or not Niedzinski teaches cationic functionalization of any position other than C(3). Applicant is correct in stating that Niedzinski does not, and the Examiner regrets erroneously stating otherwise (e.g. Action of 9/17/07, page 9). However, as indicated above, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify bile acids at either of positions 3 or 24 for several reasons:

1) Niedzinski taught modification at position 3;

2) Gebeyehu taught modification at position 24;

3) Niedzinski taught that modification of cholic acid at either position 23 or 24 did not affect uptake by receptors; and

4) even in the absence of receptors, one of ordinary skill could have reasonably expected nucleic acid uptake due to the hydrophobic character of the cationized bile salts or sterols.

In the paragraph bridging pages 8 and 9 of the Brief, Appellant argues that a "proper analysis of the scope of the instant claims makes it clear that the C(3) position is unmodified in all members of the claimed group." Appellant states that derivatizing C(3) would render the group members equivalent. This is incorrect. A proper analysis of the scope of the claims reveals no limitation regarding position C(3), and the specification at page 13, line 2 explicitly indicates that conjugation of the polycationic peptide to the bile salt is made through the hydroxyl at C(3). Furthermore, the only way the specification teaches to modify group members cholestanol and coprostanol is through C(3), because these sterols lack any other hydroxyl or carboxyl group. Accordingly, the claims clearly embrace modification at position C(3). Applicant's statement that derivatizing at C(3) would render the group members equivalent is not understood. If Applicant means that modification at C(3) would not render the group members identical, this is incorrect because various group members differ in the number and position of hydroxyl, methyl, and carboxyl groups attached to the steroid nuclease.

At page 9 of the Brief, Appellant argues that one of skill recognizes that the C(3)-modified molecules of Niedzinski are only useful as an additive to other transfection agents and that they not are "biologically functional equivalents to the un-C(3)-functionalized molecules used in the instantly claimed method." This is unpersuasive because the instant claims are not limited to "un-C(3)-functionalized molecules". As discussed above, the instant claims clearly read on modification at C(3), and in the cases of coprostanol and cholestanol, require it.

Appellant argues that the claimed methods are different because the claimed conjugates function as transfection agents without the addition of colipids, whereas the conjugate of Niedzinski was used only as a colipid. This is unpersuasive because the instant claims do not exclude the use of any colipid, and because there is no evidence of record that the conjugates of Niedzinski would not function in the absence of a colipid. The fact that they were not tested in the absence of a colipid does not mean that they would not function without one.

Appellant argues at page 10 of the Brief that the bile acids of Keener are not known material based on suitability for intended use according to Niedzinski, because Niedzinski allegedly teaches a requirement for C(3) functionalization and colipids. This is unpersuasive. Niedzinski does not "require" either C(3) functionalization or colipids, Niedzinski exemplifies these. Moreover, the cited references must be considered for all that they fairly teach. As discussed above, one of ordinary skill would have reasonably expected the bile acids of Keener to function in the method of Niedzinski because, as bile acids, they would have been recognized by the enterohepatic receptors targeted by

Niedzinski. However, one of ordinary skill would also have recognized that, even in the absence of receptors, the cholic acid moiety of Niedzinski and the hydrophobic moieties of Keener and Gebeyehu were art recognized equivalents as hydrophobic groups in conjugates designed to facilitate the delivery of hydrophilic compounds into cells. Note that both Keener and Gebeyehu taught that cholic acid could be used as a hydrophobic moiety for facilitating cellular entry of a hydrophilic molecule (a protein in the case of Keener, and nucleic acids, proteins and other macromolecules in the case of Gebeyehu). Keener indicated that bile acids and sterols were preferred hydrophobic groups, and explicitly listed cholic acid and most of the rest of the instantly claimed groups (column 19, lines 37-55). Gebeyehu indicated that steroids were acceptable hydrophobic groups, and exemplified cholic acid and two sterols, stigmasterol and ergosterol (column 9, line 58 to column 10, line 10. Thus it was abundantly clear to those of ordinary skill at the time of the invention that bile acids and sterols were useful as hydrophobic groups for the purpose of transporting hydrophilic groups into cells. Accordingly, one of ordinary skill could have combined the elements as set forth in the rejection by known methods and could have reasonably expected them to function in the intended manner. The resulting combination would have yielded predictable results to one of ordinary skill at the time of the invention.

At pages 10 and 11 of the Brief Applicant addresses the Gebeyehu reference individually, alleging that it was “cited merely for the proposition that polyamines and cationic peptides are art recognized equivalents.” Applicant concludes that Gebeyehu fails to correct the deficiencies of Niedzinski and Keener in teaching group A-R_1. This

argument fails to overcome the rejection because only the cited references clearly render obvious A- R_1 for the reasons set forth above.

At pages 11 and 12 of the Brief Appellant addresses the rejection of claims 15 and 16, arguing that neither Perrie nor the other references teach or suggest the instantly claimed conjugating agent as part of a pharmaceutical composition with or without a therapeutic compound. This is unpersuasive for the reasons set forth above, i.e. the claimed pharmaceutical composition is obvious over the combination of Niedzinski, Keener, and Gebeyehu. Perrie taught the therapeutic compound. Applicant has provided no evidence or logic to indicate that the Perrie is not combinable with the other references.

Appellant addresses the rejection of claims 11, 12, and 15 at pages 12-14 of the Brief. Appellant argues that one of ordinary skill would not believe that the conjugates of Niedzinski could be substituted for any cationic lipid such as LIPOFECTIN. The rejection as stated in the Final Action of 9/17/2007 indicated that it would have been obvious to use the cationic lipid of Niedzinski as modified by Keener and Gebeyehu in the method of Kitadai, and that the cationic lipid could be substituted for, or added to such cationic lipids as DOTMA and DOPE. Note that LIPOFECTIN is a combination of DOTMA and DOPE. Niedzinski at Table 2 and Fig. 4 on page 726 showed that various combinations of cholate conjugate with DOTAP and DOPE, or just with DOPE, resulted in protection of nucleic acids from incubation under gastric conditions. Different ratios of lipids were used, thus the cholate conjugate made up a different proportion of the total lipid in each experiment, and can be construed as having been substituted partially or

completely for the other two lipids. Clearly this experiment was performed in order to determine whether or not such combinations might also be useful for delivery to gut cells. There is no reason of record to assume that the addition the cholate lipid would interfere with the transfection efficiency of the DOTAP/DOPE mixtures. Accordingly it would have been obvious to perform similar experiments with DOTMA/DOPE (LIPOFECTIN) mixtures, and it would have been obvious to one of ordinary skill in the art at the time of the invention to use the cationic lipid conjugate of Niedzinski as modified by Keener and Gebeyehu, to substitute for DOTMA or DOPE, completely or partially, in the method of Kitadai. Further, it would have been obvious to substitute the DMDHP/cholate conjugate, as modified by Keener and Gebeyehu, for the LIPOFECTIN of Kitadai because it was abundantly clear that both compositions were intended for transfections of cells and could be used interchangeably with a reasonable expectation of success.

Appellant has not addressed why it would not have been obvious to add the conjugate of Niedzinski as modified by Keener and Gebeyehu to the LIPOFECTIN of Kitadai, particularly in view of the teaching in Niedzinski that "cholate 5 may be suitable for addition to a therapeutic lipoplex preparation" (sentence bridging pages 725 and 726.

For these reasons the rejections are maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,
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